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(54) BASE FOR PERCUTANEOUS ABSORPTION AND PERCUTANEOUSLY ABSORBABLE PREPARATION CONTAINING THE SAME

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain the subject base good in the solubility, stability and skin infiltrativity of the medicinal ingredient, low in skin irritancy, and stable in physical properties, by including a styrene-isoprene-styrene block copolymer, hexylene glycol, etc.
SOLUTION: This base for percutaneous absorption contains (A) 10-30 wt.% of a styrene-isoprene-styrene block copolymer, (B) 10-60 wt.% of a softening agent such as liquid paraffin, (C) 20-60 wt.% of a tackifying resin such as alicyclic saturated hydrocarbon resin, and (D) 1-10 wt.% of hexylene glycol. The medicinal ingredient for this base is an estrogen such as estradiol or progesterone such as norethisterone acetate at a level of 0.1-10 wt.%, being used as a cataplasm for virtually anhydrous plasters.

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* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1] A styrene-isoprene-styrene block copolymer, a softener, a tackifier, and the basis for percutaneous absorption that comes to contain hexylene glycol.
[Claim 2] The basis for percutaneous absorption according to claim 1 whose content of hexylene glycol is 1 - 10 % of the weight.
[Claim 3] The basis for percutaneous absorption according to claim 1 or 2 which a softener contains [a styrene-isoprene-styrene block copolymer] ten to 30% of the weight, and 20 - 60 % of the weight and hexylene glycol come for a tackifier to contain one to 10% of the weight ten to 60% of the weight to the pharmaceutical preparation whole quantity.
[Claim 4] The basis for percutaneous absorption given in any 1 term of claims 1-3 whose hexylene glycols are the absorption enhancers and/or the resolvent of a drug.
[Claim 5] Percutaneous absorption pharmaceutical preparation which comes to contain a drug in the basis for percutaneous absorption given in any 1 term of claims 1-4.
[Claim 6] Percutaneous absorption pharmaceutical preparation according to claim 5 which comes to blend a drug 0.1 to 10% of the weight.
[Claim 7] Percutaneous absorption pharmaceutical preparation according to claim 5 or 6 whose drugs are estrogen and/or corpus luteal hormone.
[Claim 8] Percutaneous absorption pharmaceutical preparation according to claim 7 whose estrogen is estradiol and its derivative and the loadings of whose are 0.1 - 5 % of the weight.
[Claim 9] Percutaneous absorption pharmaceutical preparation according to claim 7 whose corpus luteal hormone is norethisterone, acetic-acid norethisterone, and its derivative and the loadings of whose are 0.5 - 10 % of the weight.

[Translation done.]

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] It is related with the percutaneous absorption pharmaceutical preparation which this invention is the percutaneous absorption pharmaceutical preparation which made the solubility and skin permeability of a drug good about the field of endermic medication by using a styrene-isoprene-styrene block copolymer, a softener, a tackifier, and hexylene glycol for a basis component, and is characterized by the drugs of a quantum being certainly [correctly and] applicable to a patient beforehand.
[0002]
[Description of the Prior Art] The estradiol contained in estrogen is secreted from the ovary at the stage when it can reproduce female. Therefore, the woman before and behind a menopause mainly causes lack of estradiol, and symptoms, such as menopausal disorders and an emmeniopathy, produce her. Although the cure by oral agent administration etc. is performed for the purpose which improves these symptoms now, since alimentary canals, liver, etc., such as the stomach and intestines, are metabolized quickly and inactivation is carried out, in order to expect sufficient drug effect manifestation, high-dose estradiol must be taken. Moreover, there is a possibility that manifestation nature, such as a side effect, may increase for a high dose. Then, the attempt with which is going to lessen the metabolic turnover of estradiol by dermal administration, and tends to be made to reach into blood, and it is going to present a therapy is made. Examination which is made to absorb from transderma the corpus luteal hormone which is other hormone on the other hand, and suppresses the side effect in estradiol administration is also made. The percutaneous absorption pharmaceutical preparation which uses estradiol and corpus luteal hormone as a drug effect component at JP,4-342532,A, and uses as a principal component the acrylic binder which consists of 2-ethylhexyl acrylate and an N-vinyl-2-pyrrolidone as a binder is proposed. However, drug release nature is low, and the stimulus to the skin of an acrylic binder is strong, and it is intolerable to long-term repetitive administration.
[0003] Moreover, the gel which consists of hydroxypropylcellulose and ethanol is made to dissolve the estradiol and acetic-acid norethisterone which are a drug effect component in JP,6-51623,B, this is made into a reservoir mold, and the approach of controlling emission of a drug effect component by the permeability accommodation film is proposed. However, ethanol had a problem in side effects, like the rubor arises by the frequency where skin irritation is strong and high to a pasting part etc. The percutaneous absorption patches which become the international public presentation WO 91/No. 17752 official report and JP,5-148145,A from the styrene-isoprene-styrene block copolymer which used crotamiton as a resolvent on the other hand are proposed. However, when crotamiton was used for the resolvent, the problem was in stability -- the cohesive force which the styrene-isoprene-styrene block copolymer itself was dissolved in crotamiton, and was expected is not acquired.
[0004] Hexylene glycol (generic name.) The 2-methyl -2 and 4-pentanediol are usually used for softeners, such as a moisturizer, a solvent, an industrial use cleaning agent, a water pressure fluid, and leather fiber, and a softening agent, the agent for ink, the agent for photographs, etc. for a chemical name. The external preparations which used hexylene glycol as an antimicrobial

agent are proposed by JP,7-109220,A and JP,8-53338,A.
[0005] Moreover, the external preparations which used hexylene glycol as absorption enhancers are proposed by the international public presentation WO 96/No. 19976 official report and JP,7-138153,A. However, hexylene glycol needed to blend hexylene glycol so much, in order to acquire absorption facilitatory effect with it. [high compatibility with an acrylic basis, and] [sufficient] Furthermore, problems, such as bringing about effect, were in the adhesive fall by abundant combination of hexylene glycol, and the fundamental physical properties of pharmaceutical preparation.
[0006]
[Problem(s) to be Solved by the Invention] the above trouble -- taking an example -- the improvement 3 in skin permeability [persons / this invention] of the improvement 2 drug-effect component of the solubility of 1 drug effect component and stability -- as a result of continuing examination wholeheartedly for the purpose of offering the percutaneous absorption pharmaceutical preparation or the basis aiming at stabilization of low skin stimulus 4 basis physical properties, it results in completion of this invention.
[0007]
[Means for Solving the Problem] this invention persons resulted in header this invention that stabilization of good cohesive force and physical properties and the basis for percutaneous absorption which made good further the solubility of a drug and stability, and skin permeability were obtained by using a styrene-isoprene-styrene block copolymer, a softener, a tackifier, and hexylene glycol as a basis component, as a result of repeating research wholeheartedly, in order to solve the above-mentioned technical problem.
[0008] This invention relates to the basis for percutaneous absorption which comes to contain the hexylene glycol of sufficient amount to dissolve a styrene-isoprene-styrene block copolymer, a softener, a tackifier and sufficient amount to have a percutaneous absorption promotion operation, or a drug. Moreover, this invention relates to the percutaneous absorption pharmaceutical preparation which comes to contain a drug and the basis for percutaneous absorption. This invention relates to a styrene-isoprene-styrene block copolymer, a softener, a tackifier, the basis for percutaneous absorption patches that comes to contain hexylene glycol, and the basis for percutaneous absorption concerned and the percutaneous absorption patches which come to contain a drug as a basis component more at a detail. After sticking the percutaneous absorption patches of this invention to the patient skin, the drugs of an amount effective in a therapy are able to be emitted correctly and certainly, and this invention is to offer percutaneous absorption patches.
[0009]
[Embodiment of the Invention] It is necessary to have percutaneous absorption by the activity matter physiologically about the drug used as the active principle of the percutaneous absorption pharmaceutical preparation of this invention. Or after percutaneous absorption is carried out, you may be the so-called prodrug as shows bioactive. Or you may be the inorganic or organic addition salt permitted pharmacologically. As a drug of the percutaneous absorption pharmaceutical preparation of this invention, female sex hormones, such as estrogen and a derivative of **********, are mentioned preferably. For example, as an active ingredient, as estrogen, although estradiol, estrone, estriol, equilin, equilenins, or those derivatives are mentioned, estradiol is mainly preferably used for the percutaneous absorption pharmaceutical preparation of this invention. Moreover, as corpus luteal hormone, although progesterone, hydroxyprogesterone caproate, medroxyprogesterone acetate, dydrogesterone, chlormadinone acetate, the ethisterone, the dimethisterone, norethisterone, acetic-acid norethisterone, enanthic acid norethisterone, acetic-acid ethynodiol, the megestrol acetate, or allylestrenol is mentioned, acetic-acid norethisterone is mainly preferably used for the percutaneous absorption pharmaceutical preparation of this invention.
[0010] in addition -- as a drug effective in the percutaneous absorption pharmaceutical preparation of this invention -- for example, an antiemetic drug (example: -- granisetron --) Pollakiuria therapy agents, such as AZASE TRON, ondansetron, and RAMOSE-TRON (example: oxybutynin etc.), Angiotensin I conversion enzyme inhibitor (example: captopril, delapril), calcium

antagonists (example: nifedipine etc.) and a coronary vasodilator (example: -- diltiazem --) Local anesthetic, such as nicorandil (example: lidocaine, procaine, etc.), thymus hormone (example: factor thymique serique) and a muscle relaxant (example: -- teaser NIJIN and eperisone --) agitation psycho-stimulants, such as a dantrolene, and an anti-high-pressure agent (example: -- alprenolol --) antitumor agents, such as nifedipine, and psychotropics (example: -- an IMIPI lamin and a fentanyl --) Antibiotics, such as morphine, the anti-Parkin Son agent (example: amantadine, levodopa, etc.), An antihistamine, an anti-dizziness agent (example: diphenidol, betahistine, etc.), a mesmerism sedative and an antiphlogistic sedative drug (example: -- indomethacin, ketoprofen, and diclofenac --) Agents for autonomic nerves, such as ibuprofen, flurbiprofen, felbinac, and ketorolac, the heart and blood circulatory system drugs, and expectorant cough suppressant (example: benzothiazepine etc.) (example: -- ketotifen --) Cerebral circulation metabolic turnover improvement agents, such as tulobuterol and tranilast (example: vinpocetine etc.), a vitamin compound and the hormone drug (Lu Tina IJINGU hormone-lily JINGU hormone --) of a polypeptide system teleangiectasia agents, such as silo tropine RIRIJINGU hormone, and an immunity modifier (example: -- the poly saccharides --) Choleretic drugs, such as auranofin and lobenzarit (example: ursodesoxycholic acid etc.), The drug of classes, such as diuretics (example: hydroflumethiazide etc.), agents for diabetes mellitus (example: tolbutamide etc.), and gout drugs (example: colchicine etc.), can be used, and although it changes with combination purposes, 0.1 - 10% of the weight of loadings are usually preferably used to drugs as an amount effective in a therapy. Moreover, when un-arranging according to an interaction does not arise, two or more kinds of concomitant use is also possible for these drugs if needed.

[0011] a lot of drugs which are not considered by the conventional rubber system basis are made to contain, and the styrene-isoprene-styrene block copolymer in the agent for percutaneous absorption radicals of this invention, a softener, a tackifier, and the combination of hexylene glycol can be dealt in them -- becoming -- moreover -- acrylic -- if independent, emission of the high drug which is not obtained can be acquired. Moreover, since hexylene glycol does not dissolve substantially or can use a basis component, especially a styrene-isoprene-styrene block copolymer in the range in which the substantial dissolution is not obtained, it can acquire good cohesive force and stability.

[0012] The content to the pharmaceutical preparation whole quantity of these components is as follows. a styrene-isoprene-styrene block copolymer -- 10- 15 - 50 % of the weight and the tackifier of 15 - 25 % of the weight and a softener are [30% of the weight] 25 - 50 % of the weight still more preferably 23 to 57% of the weight 20 to 60% of the weight still more preferably 12 to 55% of the weight ten to 60% of the weight still more preferably 13 to 27% of the weight preferably, and the combination of this range has the effectiveness of this invention most. If there are few styrene-isoprene-styrene block copolymers than the above-mentioned range, cohesive force will become inadequate, if [than the above-mentioned range] more, there will be little flexibility of pharmaceutical preparation and a problem will arise in adhesion. If there are few softeners than the above-mentioned range, there will be little flexibility of pharmaceutical preparation, a problem will arise in adhesion, and if [than the above-mentioned range] more, although flexibility becomes large, a problem will produce it in pharmaceutical preparation cohesive force. A tackifier has moderate adhesiveness and compatibility with hexylene glycol within the limits of the above. Sufficient absorption facilitatory effect by sufficient combination of hexylene glycol and hexylene glycol whose tackifier is the above if out of range is not acquired.

[0013] Although it is known that the hexylene glycol which is the component of this invention will be used as a moisturizer and an antimicrobial agent as a cosmetics raw material, it is necessary to blend amount sufficient as the absorption enhancers and/or the resolvent of a drug effect component in this invention, and the loadings are 2 - 7 % of the weight more preferably 1.5 to 8% of the weight one to 10% of the weight. One or less % of the weight of loadings is [the solubility of stabilization of basis physical properties, and a drug effect component, and an absorption facilitatory effect] insufficient, and the bleeding by hexylene glycol arises at 10-% of the weight or more.

[0014] It is more desirable to use hexylene glycol independently, without using together with other absorption enhancers or a resolvent, although the hexylene glycol blended with the basis for percutaneous absorption of this invention can also be used, being used together with other absorption enhancers and/or a resolvent. absorption of a drug is not affected, although the percutaneous absorption pharmaceutical preparation of this invention has desirable patches, and the percutaneous absorption patches of this invention will come out enough on a base material if the drug content layer which consists of a drug and a basis for percutaneous absorption is substantially prepared as a monolayer -- if it becomes, other layers can be prepared and it can also consider as a multilayer. The anhydrous plaster of the pharmaceutical form of the percutaneous absorption patches of this invention is desirable especially substantially [plaster] desirable.
[0015] As a styrene-isoprene-styrene block copolymer, the styrene-isoprene-styrene block copolymer made from for example, shell chemistry (trade name: caliph REXX TR-1107, caliph REXX TR-1111), the styrene-isoprene-styrene block copolymer (trade name: JSR5000, JSR5100) by Japan Synthetic Rubber Co., Ltd., the styrene-isoprene-styrene block copolymer (trade name: Queen tuck 3421) by Nippon Zeon Co., Ltd., etc. are mentioned.
[0016] As a softener, softeners, such as a liquid paraffin, polybutene, castor oil, cotton seed oil, palm oil, palm oil, and process oil, are illustrated. As a tackifier, tackifiers, such as alicycle group saturated hydrocarbon resin (for example, Al Cong P-100 (trade name)), rosin ester (for example, KE-311, KE-100 (trade name), super ester S-100 (trade name)), a hydrogen alicycle group system hydrocarbon (for example, S KORETTSU 5300 (trade name)), terpene system hydrogenation resin (for example, chestnut ARON P-105 (trade name)), and hydrogenation rosin ester (for example, FORARU 105 (trade name)), are illustrated.
[0017] Next, the film used as the base material of this invention needs to have properties, such as excelling in the so-called barrier property for prevention of exsorption, vaporization, and adsorption of drugs. Moreover, it is desirable that there is moderate flexibility at the time of sticking equipment on the skin. Although especially limitation will not be carried out as a material of a base material if it has the above-mentioned conditions, aluminum, an ethylene vinyl acetate copolymer or its saponification object, cellulose acetate, a cellulose, nylon, polyester, polyethylene, a polyvinylidene chloride, a polycarbonate, polyvinyl alcohol, polypropylene, etc. are specifically raised as an example. These materials can carry out the laminating of what made the shape of a film or was made paper and blanket-like if needed to a film, can process it in the shape of a laminated film, or can process the vacuum plating of aluminium, ceramic vacuum evaporationo, etc., and can improve barrier property etc.
[0018] About the film used as a separator layer, it must be required during preservation of equipment to be able to prevent the exsorption vaporization from a drugs layer etc., and exfoliation removal must be possible for this separator layer in the case of use of equipment. The material of a separator film has aluminum, a cellulose, polyester, polyethylene, usable polypropylene, etc., and may specifically carry out the laminating of these films if needed. Moreover, the front face is processed by silicon or fluorocarbon, or a well-known additive is blended into a liner material, detachability may be adjusted or barrier property may be adjusted. The tongue section for exfoliation can be prepared in a separator so that the handling at the time of exfoliating may become easy.
[0019] Furthermore, a well-known additive can be blended if needed for preparation of an adhesive property, safety, and stability. Specifically Anti-oxidants, such as binders, such as a polyisobutylene, or adhesives, and dibutylhydroxytoluene, SUMIKAGERU SP-520 (trade name), AKUA keeping 10SH (trade name), Water absorbing polymers, such as ARASOBU 800F (trade name) and SANWETTO 1M-1000MPS (trade name), Inorganic bulking agents, such as a zinc oxide, a calcium carbonate, a titanium dioxide, and silicas, Optimum dose content of citric-acid triethyl, a polyethylene glycol, the glycerol, etc. is suitably carried out as fatty alcohol, such as a cull call (trade name), and a moisturizer as a dissolution assistant as absorption enhancers, such as a glycerine fatty acid ester, crotamiton, etc., such as EKISERU (trade name).
[0020] Next, the manufacture approach of the percutaneous absorption pharmaceutical preparation of this invention is explained. or [making it with a product by adding a drug effect

component and hexylene glycol, mixing to homogeneity, covering at an after / **** / liner to the above-mentioned base material if needed, and cutting in a desired configuration, after the percutaneous-absorption pharmaceutical preparation of this invention carries out the heating dissolution of for example, a drug effect component and all the basis components except hexylene glycol] -- or a sticking-by-pressure imprint can be carried out after **** at a suitable base material at the film with which exfoliation processing was once performed, and it can also make with a product. Moreover, after dissolving all components in organic solvents, such as a hexane, toluene, and ethyl acetate, after **** and an organic solvent are removed to the above-mentioned base material, and it covers at a liner, cuts in a desired configuration, and makes with a product, or an organic solvent can be removed after **** on the film with which exfoliation processing was once performed, a sticking-by-pressure imprint can be carried out at a suitable base material, and it can also make with a product.

[0021]

[Effect of the Invention] Thus, preferably, percutaneous absorption patches raise the solubility of a drug effect component and stability, and skin permeability, and have the percutaneous absorption pharmaceutical preparation of obtained this invention, and the effectiveness of stabilization of the good cohesive force of a basis, and physical properties. A merit since the degree of freedom of a drugs presentation is high, when the percutaneous absorption pharmaceutical preparation of this invention designs stability and effectiveness suitably is large.

[0022]

[Example] Although an example and the example of a trial are given and the percutaneous absorption patches of this invention are hereafter explained more to a detail, this invention is not limited to these examples. In addition, all the numeric values of an example and the example of a comparison are weight %s.

[0023]

Example 1 Styrene-isoprene-styrene block copolymer 10 Liquid paraffin 60 Tackifier (alicycle group saturated-hydrocarbon resin 20 trade name: Al Cong P-100)
A polyisobutylene 7.4 Hexylene glycol 1 Dibutylhydroxytoluene 1 Estradiol 0.1 Acetic-acid norethisterone 0.5 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.

[0024]

An example 2 A styrene-isoprene-styrene block copolymer 30 A liquid paraffin 10 Tackifier (rosin-ester trade name: KE-311) 24 A polyisobutylene 10 Hexylene glycol 10 dibutylhydroxytoluene 1 Estradiol 5 Acetic-acid norethisterone 10 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.

[0025]

An example 3 A styrene-isoprene-styrene block copolymer 20 A liquid paraffin 29 Tackifier () [hydrogenation rosin ester] 30 Trade name : FORARU 105 A polyisobutylene 10 Hexylene glycol 7 Dibutylhydroxytoluene 1 estradiol 1 Acetic-acid norethisterone 2 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.

[0026]

Example 4 Styrene-isoprene-styrene block copolymer 20 Liquid paraffin 35 Tackifier (hydrogenation rosin-ester 30 trade name: FORARU 105)
A polyisobutylene 10 Hexylene glycol 1 Dibutylhydroxytoluene 1 Estradiol 1 Acetic-acid norethisterone 2 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.

[0027]

Example 5 Styrene-isoprene-styrene block copolymer 20 Liquid paraffin 24 Tackifier (hydrogenation rosin-ester 30 trade name: FORARU 105)
A polyisobutylene 12 Hexylene glycol 10 Dibutylhydroxytoluene 1 Estradiol 1 Acetic-acid

norethisterone 2 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.
[0028]
Example 6 Styrene-isoprene-styrene block copolymer 20 Liquid paraffin 21 Tackifier (hydrogenation rosin-ester 25 trade name: FORARU 105)
A polyisobutylene 10 Hexylene glycol 8 Dibutylhydroxytoluene 1 Estradiol 5 Acetic-acid norethisterone 10 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.
[0029]
An example 7 A styrene-isoprene-styrene block copolymer 15 A liquid paraffin 15 Tackifier () [hydrogenation rosin ester] 60 Trade name : FORARU 105 A polyisobutylene 7.4 Hexylene glycol 1 Dibutylhydroxytoluene 1 estradiol 0.1 Acetic-acid norethisterone 0.5 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.
[0030]
An example 8 A styrene-isoprene-styrene block copolymer 20 A liquid paraffin 30 Tackifier () [hydrogenation rosin ester] 30 Trade name : FORARU 105 A polyisobutylene 10 Hexylene glycol 7 Dibutylhydroxytoluene 1 Oxybutynin 2 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as oxybutynin pharmaceutical preparation.
[0031]
Example 9 Styrene-isoprene-styrene block copolymer 20 Liquid paraffin 35 Tackifier (hydrogenation rosin-ester 30 trade name: FORARU 105)
A polyisobutylene 10 Hexylene glycol 1 Dibutylhydroxytoluene 1 Teaser NIJIN 3 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as teaser NIJIN pharmaceutical preparation.
[0032]
Example 10 Styrene-isoprene-styrene block copolymer 20 Liquid paraffin 24 Tackifier (hydrogenation rosin-ester 30 trade name: FORARU 105)
A polyisobutylene 12 Hexylene glycol 10 Dibutylhydroxytoluene 1 Ketoprofen 3 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as ketoprofen pharmaceutical preparation.
[0033]
Example 11 Styrene-isoprene-styrene block copolymer 20 Liquid paraffin 28 Tackifier (hydrogenation rosin-ester 25 trade name: FORARU 105)
A polyisobutylene 15 Hexylene glycol 8 Dibutylhydroxytoluene 1 Granisetron 3 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as granisetron pharmaceutical preparation.
[0034]
An example 12 A styrene-isoprene-styrene block copolymer 15 A liquid paraffin 15 Tackifier () [hydrogenation rosin ester] 58.6 Trade name : FORARU 105 A polyisobutylene 7.4 Hexylene glycol 1 Dibutylhydroxytoluene 1 Tulobuterol 2 According to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as tulobuterol pharmaceutical preparation.
[0035]
The example 1 (hexylene glycol un-blending) of a comparison
Styrene-isoprene-styrene block copolymer 20 Liquid paraffin 36 Tackifier (hydrogenation rosin-ester 30 trade name: FORARU 105)
A polyisobutylene 10 Dibutylhydroxytoluene 1 Estradiol 1 Acetic-acid norethisterone 2 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.

[0036]
The example 2 (resolvent crotamiton) of a comparison
Styrene-isoprene-styrene block copolymer 20 Liquid paraffin 29 Tackifier (hydrogenation rosin-ester 30 trade name: FORARU 105)
A polyisobutylene 10 Crotamiton 7 Dibutylhydroxytoluene 1 Estradiol 1 Acetic-acid norethisterone 2 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.
[0037]
The example 3 (acrylic basis) of a comparison
TS-620 (methyl-acrylate 2-ethylhexyl-acrylate 89 copolymerization resin emulsion: product made from Japanese carbide)
hexylene glycol 8 Estradiol 1 Acetic-acid norethisterone 2 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.
[0038]
Example 4 of a comparison Styrene-isoprene-styrene block copolymer 5 Liquid paraffin 65 Tackifier (hydrogenation rosin-ester 10 trade name: FORARU 105)
A polyisobutylene 3.4 Hexylene glycol 15 Dibutylhydroxytoluene 1 Estradiol 0.1 Acetic-acid norethisterone 0.5 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.
[0039]
Example 5 of a comparison Styrene-isoprene-styrene block copolymer 35 Liquid paraffin 5 Tackifier (hydrogenation rosin-ester 32 trade name: FORARU 105)
A polyisobutylene 3 Hexylene glycol 7 Dibutylhydroxytoluene 1 Estradiol 6 Acetic-acid norethisterone 11 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.
[0040]
Example 6 of a comparison Styrene-isoprene-styrene block copolymer 20 Liquid paraffin 29 Tackifier (hydrogenation rosin-ester 36.5 trade name: FORARU 105)
A polyisobutylene 10 Hexylene glycol 0.5 Dibutylhydroxytoluene 1 Estradiol 1 Acetic-acid norethisterone 2 -- according to the above-mentioned manufacture approach, it produced by this formula, it cut in desired magnitude, and considered as estradiol and acetic-acid norethisterone mixing pharmaceutical preparation.
[0041] 50 degrees of each test piece of the dissolution stability test examples 1, 2, 3, 4, 5, 6, and 7 of the drug effect component to an example of the example trial of trial 1. basis and the examples 1, 4, and 6 of a comparison were saved for C.3 months, and the crystal deposit or bleeding from each test piece was observed. The result is shown in Table 1. The deposit of a crystal was observed in the examples 1 and 6 of a comparison. The bleeding of hexylene glycol was observed by the example 4 of a comparison. A deposit of a crystal and bleeding were not observed by the example.
[0042]
[Table 1]

	結晶化観察 50°C・3M	ﾌﾟﾘｰﾃﾞｨﾝｸﾞの観察 50°C・3M
実施例 1	結晶析出なし	ﾌﾟﾘｰﾃﾞｨﾝｸﾞなし
実施例 2	結晶析出なし	ﾌﾟﾘｰﾃﾞｨﾝｸﾞなし
実施例 3	結晶析出なし	ﾌﾟﾘｰﾃﾞｨﾝｸﾞなし
実施例 4	結晶析出なし	ﾌﾟﾘｰﾃﾞｨﾝｸﾞなし
実施例 5	結晶析出なし	ﾌﾟﾘｰﾃﾞｨﾝｸﾞなし
実施例 6	結晶析出なし	ﾌﾟﾘｰﾃﾞｨﾝｸﾞなし
実施例 7	結晶析出なし	ﾌﾟﾘｰﾃﾞｨﾝｸﾞなし
比較例 1	結晶析出あり	ﾌﾟﾘｰﾃﾞｨﾝｸﾞなし
比較例 4	結晶析出なし	ﾌﾟﾘｰﾃﾞｨﾝｸﾞあり
比較例 6	結晶析出あり	ﾌﾟﾘｰﾃﾞｨﾝｸﾞなし

[0043] example of trial 2. -- 50 degrees of each test piece of the check example 3 of description and the examples 2 and 4 of a comparison were saved for C.3 months, and the appearance and description of each test piece were observed. The result is shown in Table 2. it is the flow of a basis at an example 3 -- carrying out -- although it did not accept, the flow broth of a basis was accepted in the examples 2 and 4 of a comparison.

[0044]

[Table 2]

	50°C・3M
実施例 3	変化なし
比較例 2	流れだしあり
比較例 4	流れだしあり

[0045] Hair loess mouse (6-weeks old, female) regions-of-back skin temperature (C) radiographic examination of 37 degrees was performed using the Franz mold diffusion cel per test piece of the example of trial 3. skin radiographic examination example 3, and the examples 2

and 3 of a comparison. Receptor liquid was extracted for every after [test initiation] duration, receptor liquid was filled up immediately after that, and the amount of transparency of the drug to extraction receptor liquid was measured by high-speed liquid chromatography. It made the measurement size of each test piece into three pieces at a time, respectively. A result is shown in drawing 1 and 2. The example 3 reached and showed good drug permeability as compared with the examples 2 and 3 of a comparison.

[0046] The emission trial was performed by the rotating-cylinder method per test piece of the example of trial 4. emission trial example 3, and the examples 1 and 6 of a comparison. As a test condition, it is 32.0 **0.5-degreeC whenever [900ml / of test fluid /, and trial solution temperature]. It carried out by cylinder rotational frequency 50rpm. A result is shown in drawing 3 and 4. Trial of the examples 1 and 6 of a comparison In the example 3, emission of a good drug effect component was acquired to the piece of **.

[0047] The adhesion test was performed by the following technique per test piece of the test piece of the example of trial 5. adhesion test examples 1, 2, and 3, and the examples 4 and 5 of a comparison. The posterior matter arrival nature which stuck the test piece on ten test subjects' (healthy people, male) overarm section, and was stuck on it for 24 hours was evaluated. The result is shown in Table 3. Although or more 1/2 exfoliation was seen by most in the example of a comparison, in the example, those without exfoliation were almost the case.

[0048]

[Table 3]

	剥離なし	ｴｯｼﾞ剥離	1/4	1/2	3/4	脱落	合計(人)
実施例1	9	-	1	-	-	-	10
実施例2	8	1	1	-	-	-	10
実施例3	9	1	-	-	-	-	10
比較例4	-	-	-	1	3	6	10
比較例5	-	-	1	7	1	1	10

[0049]

[Effect of the Invention] According to this invention, stabilization of good cohesive force and physical properties, the basis for the percutaneous absorption which made good further the solubility of a drug and stability, and skin permeability, and the percutaneous absorption pharmaceutical preparation using it can be offered by using a styrene-isoprene-styrene block copolymer, a softener, a tackifier, and hexylene glycol as a basis component.

[Translation done.]